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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/596,267	02/07/2007	Gaetano Giammona	1108.1003	4701

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EXAMINER	
BROWE, DAVID	

ART UNIT	PAPER NUMBER
4131	

NOTIFICATION DATE	DELIVERY MODE
07/27/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

info@lmiplaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/596,267	GIAMMONA ET AL.	
	Examiner	Art Unit	
	DAVID M. BROWE	4131	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-7* is/are rejected.

7)☒ Claim(s) *4 and 8-19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :June 19, 2006 and November 13, 2006.

DETAILED ACTION

Claims 1-19 are pending.

Foreign Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. RM2004A000168, filed on April 1, 2004.

Abstract

The abstract is objected to for the following reasons: 1) Abstract is too short and not sufficiently descriptive of the invention. The abstract should be within the range of 50 to 150 words. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details. 2) Abstract contains legal phraseology. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. Appropriate correction is required.

Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include a cross-reference to related applications on the first page below the title.

Claim Objections

Claims 4 and 8-19 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only, and cannot depend from any other multiple dependent claim. See MPEP

§ 608.01(n). **Accordingly, claims 4 and 8-19 have not been further treated on the merits.**

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bromberg *et al.* (U.S. Patent Application Pub. No. 20030152623), in view of Gupta *et al.* (Drug Discovery Today, 2002), Blum *et al.* (U.S.Patent No. 6,294,591), and Giammona *et al.* (Biochemica et Biophysica Acta, 1999).

Applicant Claims

Applicants claim an anionic hydrogel matrix obtained by irradiation-induced cross-linking of modified copolymers that have been suitably derivatised in the presence of acid co-monomers. In addition to using a variety of standard biocompatible polymers well known in the art, applicants specify that the hydrogel matrix can also be synthesized from poly(N-2-hydroxyethyl)D,L-aspartamide (PHEA). Suitably derivatised polymers can be cross-linked by gamma rays, beta rays, and ultraviolet radiation in the presence of methacrylic acid or acrylic acid comonomers to generate a hydrogel matrix preferably in the form of a microparticle, or, alternatively, in the form of a nanoparticle, gel, film, cylinder, or sponge.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Bromberg *et al.* disclose a microgel which consists of a chemically cross-linked ionizable network in the form of microspherical particles that comprises at least one therapeutic active ingredient, and reversibly responds to a change in aqueous conditions, such as pH, by swelling (Pg. 4, secs. 0038-0039, 0041; Pg. 25, sec. 0193). Poly-anion forming compounds that can be cross-linked into an anionic microgel matrix can include polyaminoacid polymers, acrylic and methacrylic acid polymers, vinyl

polymers, carboxyalkyl cellulose, polysaccharides, dextrins, pectins, synthetic or natural rubbers and alginic acid (Pg. 5, secs. 0050-0052). The microgels are particularly suited for use in the medical and veterinary fields for oral, topical, parenteral, and vaginal administration (Pg. 21, sec. 0136; Pg. 24, secs. 0182, 0184-0185).

Gupta *et al.* disclose that the general use of hydrogels as stimuli-responsive, particularly pH-responsive, controlled-release polymeric drug delivery systems for biomedical and pharmaceutical applications is a concept well established in the art. Hydrogels exhibit stimuli-responsive changes in their structural network, such as pH-responsive swelling, that cause release of entrapped drug. The change in hydrogel structure, and drug release, can be completely reversible upon removal of the stimulus. Hydrogels can serve as drug delivery systems for oral, nasal, buccal, rectal, vaginal, ocular, and parenteral routes of administration. Hydrogels are often prepared by chemical, physical or radiation cross-linking polymers containing hydroxyl, amine, amide, ether, carboxylate and sulfonate as functional groups in their side chains. The design of a hydrogel-based dosage form depends on the route of administration, and can take on any desired shape and characteristic suitable for the application, including nano- or micro-sized spherical beads, cylinders, discs, and torpedo-shaped sponges. Anionic hydrogels can be composed of any polymer whose backbones have pendant groups that are un-ionized below and ionized above the pKa of the polymeric network. In aqueous media with a pH above the polymer pKa, the pendant groups ionize generating electrostatic repulsive forces, which leads to swelling of the hydrogel, and , usually, concurrent release of the entrapped drug(s).

Blum *et al.* disclose a general process for modifying polymers via a polymer-analogous reaction by introducing double bonds and ester groups into their structure enabling said polymers to be cross-linked by radiation to form a cured network (Col. 1, lns. 6-7; Col. 3, lns. 66-67; Col. 4, lns. 1-2). This process is achieved by reacting acrylate or methacrylate copolymers with a suitable compound, whose side group can react with the copolymer side group(s) in a condensation or addition reaction and can form free radicals under the action of actinic radiation (Col. 1, lns. 63-68; Col. 2, lns. 1-3). The polymers can be derivatised in this manner by reacting methacrylic acid or acrylic acid with glycidyl methacrylate (GMA) or methacrylic anhydride (MA) (Col. 4, lns. 4-10). Actinic, or chemically-active, radiation, used to induce suitably derivatised polymer cross-linking includes gamma rays, beta rays (e. g. electron beams), and ultraviolet radiation (Col. 2, lns. 8-11).

Giammona *et al.* disclose that the specific polymer, poly(N-2-hydroxyethyl)D,L-aspartamide (PHEA) can be derivatised using GMA in the general manner described by Blum *et al.*, and subsequently cross-linked by ultraviolet irradiation to form an anionic biodegradable hydrogel matrix. Such biodegradable hydrogels are of interest in the area of controlled drug delivery.

Ascertainment of the Difference Between the Scope of the Prior Art and the Claims (MPEP §2141.012)

Bromberg *et al.* disclose a stimulus-responsive anionic hydrogel matrix in the form of microparticles obtained by chemically-induced cross-linking of a variety of standard biocompatible polymers known in the art. The anionic hydrogel matrices can

be loaded with one or more therapeutic or cosmetic active ingredients, and additionally one or more pharmaceutically acceptable excipients, and used as a controlled-release drug delivery system in the medical or veterinary fields, to be administered by oral, parenteral, or vaginal routes, for the treatment of tumours, or for the treatment of cardiovascular, nervous system, or intestinal diseases.

Bromberg *et al.*, however, lack the explicit teaching that the anionic hydrogel matrices can take on a variety of desired forms, such as cylinders, and that they can generally be obtained by irradiation-induced cross-linking of modified copolymers that have been suitably derivatised, and in particular from PHEA modified by side chain reactions with agents such as, for example, GMA and/or MA. This deficiency is cured by Gupta *et al.*, Blum *et al.*, and Giammona *et al.*, who teach, respectively, that anionic hydrogel synthesis by irradiation-induced cross-linking is a well known concept and practice in the art, that irradiation-induced cross-linking can generally be accomplished using modified polymers suitably derivatised with agents such as GMA and/or MA, and that an anionic hydrogel matrix can be synthesized in particular from irradiation-induced cross-linking of PHEA suitably derivatised with an agent like GMA. Gupta *et al.* further teaches that an anionic hydrogel matrix can take on any desired shape and characteristic suitable for its intended application.

Finding of Prima Facie Obviousness Rational and Motivation

(MPEP §2142.2143)

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the present invention to combine the teachings of Bromberg *et al.*, Gupta *et al.*,

Blum *et al.*, and Giammona *et al.* to devise an anionic hydrogel matrix synthesized by irradiation-induced cross-linking of biocompatible polymers, including PHEA, suitably derivatised. Cross-linked polymer matrix synthesis traditionally required the use of toxic initiators and contaminating chemical cross-linking agents, often used unwanted or unpleasant solvent systems, and required additional laborious purification steps (Blum *et al.*, Col. 1, lns. 18-52; Giammona *et al.*); an approach not optimal for preparing products intended for medical or veterinary use. A skilled artisan, therefore, would be motivated to synthesize a stimulus-responsive hydrogel matrix for controlled-release drug delivery, as taught by Bromberg *et al.*, with the alternative approach to polymer cross-linking as taught by Blum *et al.*, using a polymer that is nontoxic and resistant to damage from the radiation employed in the cross-linking procedure, such as PHEA as taught by Giammona *et al.*, with the reasonable expectation that this approach will successfully produce a more pure and safe product with less effort, as shown previously (Blum *et al.*; Giammona *et al.*). Applicants have no allegations of surprising or unexpected results. Therefore, the claimed invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Inquiries

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DAVID M. BROWE whose telephone number is 571-270-1320. The examiner can normally be reached on Monday-Friday 7:30AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick J. Nolan can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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